Functionally Distinct Subsets of Lineage-Biased Multipotent Progenitors Control Blood Production in Normal and Regenerative Conditions.

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Public Summary:
How new blood cells of various types are made from multipotent progenitors (MPPs) remains poorly understood. Our major finding in this work, performed in mice, further characterizes the compartment containing those cells that renew all blood production in the body. We found two new distinct subsets of progenitor cells that are present together but produced independently by blood (hematopoietic) stem cells. When the body needs more myeloid cells (e.g. red blood cells), these newly identified progenitors provide the key source for this demand. Interestingly, we found that these progenitors are hard-wired to produce particular types of cells and that these progenitors are made preferentially by the stem cells when the blood needs to be reconstituted. Thus, regeneration is achieved at the expense of losing other stem cell functions such as engraftment, self-renewal, and the production of the lymphoid lineage of cells that make up the immune system. From our study we propose a “dynamic model” of blood development in which the blood stem cells exist in distinct subsets of quiescent, activated, and lineage-primed cells that represent a continuum of likely reversible states. The cells create new daughter cells depending on the needs of the body at any given moment. It will be interesting to find out whether similar sub-populations of cells also exist in humans. If so, it could offer a new option for patients to help manipulate the body to help rebalance the blood’s composition of cell types such as after the treatment with anti-cancer therapies or after bone marrow transplantation or to revitalize an aging or malfunctioning immune system.

Scientific Abstract:
Despite great advances in understanding the mechanisms underlying blood production, lineage specification at the level of multipotent progenitors (MPPs) remains poorly understood. Here, we show that MPP2 and MPP3 are distinct myeloid-biased MPP subsets that work together with lymphoid-primed MPP4 cells to control blood production. We find that all MPPs are produced in parallel by hematopoietic stem cells (HSCs), but with different kinetics and at variable levels depending on hematopoietic demands. We also show that the normally rare myeloid-biased MPPs are transiently overproduced by HSCs in regenerating conditions, hence supporting myeloid amplification to rebuild the hematopoietic system. This shift is accompanied by a reduction in self-renewal activity in regenerating HSCs and reprogramming of MPP4 fate toward the myeloid lineage. Our results support a dynamic model of blood development in which HSCs convey lineage specification through independent production of distinct lineage-biased MPP subsets that, in turn, support lineage expansion and differentiation.